Dissertation on

A STUDY ON CLINICAL OUTCOMES OF LASER PHOTOCOAGULATION FOR PREMATURE RETINOPATHY

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CERTIFICATE

This is to certify that the dissertation entitled, **"A STUDY ON CLINICAL OUTCOMES OF LASER PHOTOCOAGULATION FOR PREMATURE RETINOPATHY"** submitted by **Dr.MALATHI.V.K,** in partial fulfillment for the award of the degree of Master of Surgery in Ophthalmology by The Tamil nadu Dr.M.G.R.Medical University, Chennai is a bonafide record of the work done by her in the Regional Institute of Ophthalmology, Government Ophthalmic Hospital, Egmore, Chennai, during the academic year 2010-2013.

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Part One

RETINOPATHY OF PREMATURITY (ROP)

INTRODUCTION

ROP is a vaso-proliferative disorder of premature /preterm infants with gestational age less than 32 weeks or birth weight less than 1500gms especially those exposed to high concentration of oxygen.

The range of possible outcomes for patients with ROP extends from minimum sequelae with no effect on vision in mild cases to bilateral irreversible and total blindness in advanced cases.

In India the threshold ROP has been documented even in babies weighing 2000gram at birth. At present the cut off birth weight and gestational age need to be increased. Early diagnosis and prompt treatment with laser has proved to be effective in preventing progression of ROP in this study.

HISTORY

Retinopathy of prematurity first defined by TERRY in 1942, within a decade became the primary cause of childhood visual loss. He called it retrolental fibroplasias. As the pathogenesis was better understood the term retinopathy of prematurity was coined.

The discovery of the relationship between supplementary oxygen and ROP in 1950s led to the practice of rigid curtailment of oxygen supplementation in nursery.

During this period no clinical monitoring systems were available to measure blood oxygenation. An increase in deaths caused by respiratory distress syndrome (RDS) was reported.

By the late 1960s and early 1970s arterial blood gas analysis had come into general use and the oxygen requirements of premature infants and RDS were better documented. Arterial blood gas monitoring enabled pediatricians to titrate the incubator oxygen concentration to more nearly meet the individual premature infant’s oxygen needs.

EMBRYOLOGY

Michelson suggested that retinal capillaries arise by budding from pre existent arteries and veins that originate from hyaloids vessels at the optic nerve head. On the posterior edge of an advancing mesenchyme, a chicken wire meshwork of capillaries develops. This fine meshwork of vessels undergoes absorption and remodeling to produce mature arteries and veins. The nasal part of retina is vascularised first, around 32 weeks of gestation followed by temporal retina which vascularises at term.

PATHOGENESIS

Alon et al demonstrated that hyperoxia caused down regulation of VEGF and death of endothelial cells, suggesting that VEGF is an endothelial survival factor. In the time that follows closure of these growing vessels, the differentiating retina becomes increasingly ischemic and hypoxic and VEGF is unregulated driving neovascularisation.

The description of the mechanism of oxygen's effects given previously points out the initial changes in the developing vessels, and that historically this was believed to be an injury caused by excess oxygen.

Theoretically the provision of increased oxygen should down-regulate the release of such growth factors. This hypothesis was tested in the kitten model of oxygen induced retinopathy. Systemic mild hypoxia was found to worsen the retinopathy where as mild hyperoxia improved it. Similar results have been demonstrated in a mouse model where VEGP is clearly one of the major growth factors involved. A multicenter clinical trial studied this concept in the nursery. Results showed that once the ROP was established, raising the oxygen

saturation mildly did not harm the ROP, but neither was it of clear benefit. In general the study showed no statistical difference in the progression to severe ROP between the two oxygen treatment regimens that were tested.

The clinical and histo-pathalogical observations of Flynn and co-workers led them to postulate the following sequence of events in the development of ROP in human infants:

1. Injury to the endothelium occurs where it has just differentiated from mesenchyme to form the primitive capillary meshwork. This is reminiscent of the animal studies in which a short duration of hyperoxia resulted in capillary damage limited to the most recently differentiated vascular complexes. It is currently believed that environmental factors other than oxygen also are involved. Nitric oxide and subsequent formation of peroxynitrite can contribute to the vaso-obliterative stage of ROP. Reduced VEGF results in death of endothelial cells because of its role as a survival factor.

2. After injury to the vascular endothelium by some noxious agents, the mesenchyme and the mature Arteries and the veins survive and merge via the few remaining vascular channels to form a mesenchymal arterio- venous shunt. The shunt replaces the destroyed or damaged capillary bed.

3. The mesenchymal arterio- venous shunt is located at the demarcation between the vascular and avascular retina. Flynn suggested that this structure represents the pathognomonic lesion of acute ROP.

Flynn described a dormant period after the injury, which may last from several days to months during which the retinal findings are relatively stable. The tissue comprising the shunt may thicken, and the grey-white initial colour of the structure turns from pink to salmon red. He started that during this period when vasculogenic activity resumes in the retina, the fate of the eye is decided. Flynn pointed out that the cells inside the shunt divide and differentiates into normal capillary endothelium. They form primitive endothelial tubes that send forth a brush border of capillaries that grows anteriorly into the avascular retina. This represents involution of ROP, which he observed to occur in more than 90% of cases at this early stage.

In progressive disease however the primitive cells inside the shunt proliferate and erupt through the internal limiting membrane, growing on the surface of retina and into the vitreous body. Flynn stated, it is this lack of differentiation and destructive proliferation of cells and their invasion into spaces and tissues where they do not belong is a chief event in the process of membrane proliferation leading to tractional retinal detachment.

Foos suggested a pathogenesis of ROP based on examination of histopathologic material. He used the terms vanguard and rear-guard to describe the cellular components of the developing retina. The vanguard or anterior component contains a spindle shaped cells thought to be glia, which play a role in nourishing the immature retina during its development. The rear guard contains primitive endothelial cells. As the retina matures the endothelial cells aggregate into cords that according to Foos subsequently luminize and become the primordial capillaries of retina. It is from the rear god and primitive endothelial cells that the neovascularisation of ROP will develop.

Foos noted that as the developing vasculature reaches its most anterior extent and matures, the spindle cells of the van guard disappear. The spindle cells are endothelial precursors and in the fetal human and neonatal dog retina, the precursors organise and differentiate to form the initial retinal vasculature.

EFFECTS OF OXYGEN ON IMMATURE RETINA

Primary Effect

Retinal vasoconstriction followed by some degree of vascular closure if the oxygen supply is continued. Electron microscopic observations demonstrate selective hyperoxic injury to the endothelial cells of immature vessels without obvious changes in the neuronal elements of the retina.

Secondary Effect

Following sustained hyperoxia when the lab animal is removed to ambient air, a marked endothelial proliferation arises from the residual vascular complexes immediately adjacent to retinal capillaries ablated during hypoxia.

Nodules of proliferating endothelial cells canalise to form new vessels that not only grow within the retina, but also erupt through the internal the internal limiting membrane to grow on its surface, similar to the neovascularisation in other proliferative retinopathies .Oxygen exerts an important effect on the remodelling of the original primitive capillary network that develops in the retina.

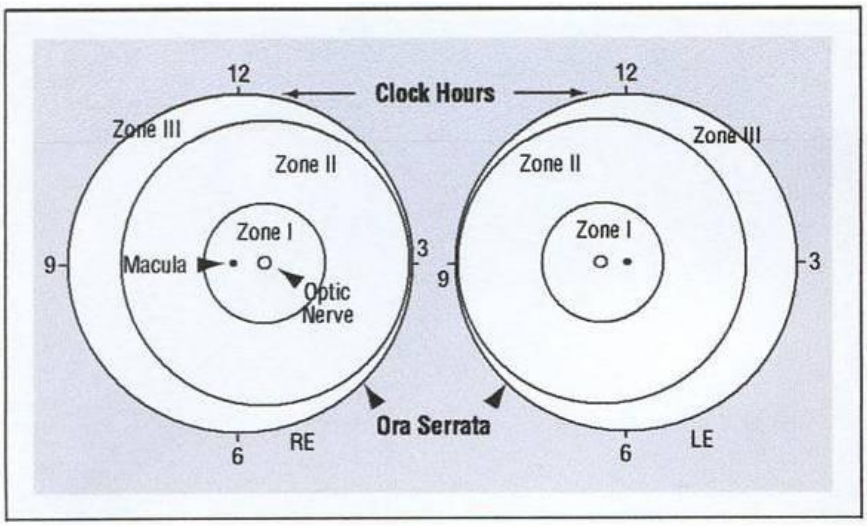
Pierce and colleagues have demonstrated the correlation of vascular endothelial growth factor(VEGF) protein production with periods of low oxygen, as well as its disappearance after oxygenation.

Other growth factors such as adenosine and IGF-1 may also be involved.

ZONES OF INVOLVED RETINA

ZONE 1

An imaginary circle with centre as the optic disc with a diameter, twice the distance from the optic nerve to the macula is zone 1. The hallmark of the disease worsening is not the presence of neovascularisation, but is by the increasing dilation and tortuosity of the vessels.



ZONE 2

Zone 2 extends from peripheral border of zone 1 to a concentric circle tangential to nasal ora serrata. Temporally this imaginary boundary corresponds to the anatomic equator.

ZONE 3

Once the nasal vessels have reached ora serrata, zone 3 is the remaining temporal crescent of retina anterior to zone 2. Zone 3, which is the farthest from the disc, is the last to get vascularised.

Aggressive disease rarely is seen in this zone. Typically, this is slowly vascularising and requires evaluations every few weeks.

Many infants show inactive disease in zone 3 with a demarcation line and non-vascularised retina. This has been noted in toddlers and can be considered cicatricial peripheral disease. No ill sequelae are known to occur from this ridge.

STAGING OF ROP

STAGE 0:

It is immature retinal vasculature without demarcation between vascularised and non-vascularised retina.

In zone 1, this may appear as a vitreous haze, with the optic nerve as the only landmark. Weekly examinations should be performed.

STAGE 1-Demarcation line:

Stage 1 is characterized by the presence of a demarcation line, the first pathognomonic ophthalmic sign of ROP. The line represents a structure separating the anterior avascular retina from the posterior vascularised retina. It is flat and white and lies within the plane of retina.

STAGE 2 – Ridge:

The demarcation line of stage 1 acquires a height and width, occupies a volume, and extends centripetally within the globe. Vessels may leave the surface of the retina to enter the ridge. Small tufts of new vessels are called popcorn lesions; these may be located posterior to the ridge.

- In zone 1, if there is a ridge, this is an ominous sign. The disease is graded as threshold if there are tortuous vessels in the posterior pole and treatment commenced within 3 days.

- In zone 2, if there are no vascular changes and the ridge has no engorgement, the eye should be examined biweekly.

- Pre-threshold is stage 2 with a plus disease.

  In zone 3, examination every 2-3 weeks should be sufficient, unless of course there is any vascular tortuosity or straightening of the vascular arcades.

STAGE 3- extra retinal fibro vascular proliferation:

The proliferating tissue causes a ragged appearance of the ridge as the proliferation increases into the vitreous.

The extra retinal fibro vascular proliferation (neovascularisation) may be present on the ridge, on the posterior surface of the ridge or anteriorly toward the vitreous cavity. The neovascularisation gives the ridge a velvety appearance, a ragged border.

- In zone 1, if there is any neovascularisation, it is serious and requires treatment.

- In zone 2, pre-threshold is defined as stage 3 without plus disease, or stage 3 with less than 5 contiguous or 8 non-contiguous hours.

- Threshold is stage 3 with at least 5 contiguous or 8 non-contiguous hours and plus disease.

- In zone 3, examination every 2-3 weeks should be sufficient, unless there is any vascular tortuosity or straightening of the vascular arcades.

STAGE 4- Subtotal retinal detachment:

This stage is a subtotal retinal detachment beginning at the ridge. The retina is pulled anteriorly into the vitreous by the fibro vascular ridge.

- Stage 4A does not involve the fovea.

- Stage 4B involves the fovea.

STAGE 5 - Total retinal detachment:

This stage is a total retinal detachment in the shape of a funnel.

- Stage 5A is an open funnel.

- Stage 5B is a closed funnel.

PLUS DISEASE

Plus disease is defined as arteriolar tortuosity and venous engorgement of the posterior pole, iris vascular engorgement, pupillary rigidity, and vitreous haze, which are part of the sub classification given to the above stages. The presence of plus disease is an ominous sign.

PRE-PLUS DISEASE

Pre-plus disease is defined as vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arteriolar tortuosity and more venular dilatation than normal. Signs of pre-plus disease early in the course of ROP were shown to be strongly associated with development of severe ROP that required laser treatment. The diagnosis of pre-plus disease adds prognostic value beyond that already known with birth weight, gestational age, ROP zone, and ROP stage.

CORRELATION OF PATHOGENESIS WITH CLINICAL CLASSIFICATION

According to Garner, the demarcation line of stage 1 ROP morphologically comprises two relative distinct zones. The anterior zone is formed by a mass of spindle shaped cells, which are the progenitors of differentiated vascular endothelium. It corresponds to the primitive mesenchyme seen in the normal fetal development but with a considerable increase in the number of cells. It is this hyperplasia, involving both thickening and widening, that makes the demarcation line visible.

The demarcation according to Garner is devoid of functioning capillaries

According to Garner the retinal ridge that characterizes stage 2 results from the proliferation of endothelial cells with organization into vascular channels.

According to Foos, the stage 3 appears as placoid, polypoid, or pedunculated. The placoid pattern is the most common and it correlates with development of retinal detachment. A condensation of vitreous body over the ridge is related to depolymerisation of hyaluronic acid and collapse of the collagenous framework into optically visible structures.

INVOLUTION OF ROP

Regressed ROP: although active ROP usually involutes without progressing to retinal detachment, cicatricial sequelae can remain even in those cases.

Patients with regressed ROP are at risk for developing strabismus and amblyopia early in life. Regular examination and attention to refractive, visual, and extra ocular muscle status are indicated for all infants who have had ROP until about age 18 months, and thereafter as clinically indicated.

OTHER TERMS MENTIONED WITH ROP INCLUDE THE FOLLOWING

- **POPCORN**

  Anterior to the internal limiting membrane a cicatrized neovascularisation is seen which is called popcorn.

- **HOT DOG**

  A red active ridge, is the site of increasing vascular channels. If noted on zone 1 or 2, this is a dangerous sign. This area may regress with cicatrix floating in the vitreous cavity.

- **RUSH DISEASE**

  This is rapidly progressing subtype of ROP which does not progress step wise from stage 1 to 5, but instead may rush to stage 5.

GLAUCOMA IN RETINOPATHY OF PREMATURITY

Patients with advanced retinopathy who develop a shallow anterior chamber develop acute or sub-acute glaucoma later. Some cases may respond to topical steroids and cycloplegic agents. Parents should be cautioned to consult an ophthalmologist if the child appears to be having sudden discomfort or irritation of the eye.

RISK FACTORS

- Low birth
- Prolonged supplemental oxygen
- Higher arterial carbon dioxide levels
- Cyanosis
- Apnoea
- Mechanical ventilation
- Intra ventricular haemorrhages
- Seizure
- Transfusions
- Septicemia
- In utero hypoxia
- Anemia
- Patent ductus arteriosus
- Vitamin E deficiency.

DIFFERENTIAL DIAGNOSIS

- Familial Exudative Vitreoretinopathy is an X-linked recessive syndrome that appears similar to ROP but occurs in full-term infants.
- Persistent foetal Vascular can cause a traction retinal detachment difficult to differentiate but typically unilateral and does not have a correlation to prematurity.
- Retinoblastoma is a differential diagnosis for stages 4 and 5 of retinopathy of prematurity presenting as leucokoria.
- Congenital cataracts
- Incontinentia pigmenti- X-linked dominant disorder manifesting pigmentary, skin abnormalities with ocular, central nervous system and dental abnormalities.
- Norrie’s disease is a congenital retinal dysplasia (X-linked recessive) mimicking advanced ROP.

ETROP FOLLOW UP CRITERIA

- Twice a week:

  Zone 2, no plus, stage 3

  Zone 1, no plus, stage 2

  Zone 1immature, no ROP

- Every 2 weeks:

  Zone 2, no plus

  Immature retina or stage 1

PROPHYLAXIS AND THERAPY

ROLE OF VITAMIN E

1. Activation of spindle cells results initially in the increase in gap junctions between adjacent spindle cells, secondarily in the increase in cytoplasmic volume of rough endoplasmic reticulum, and in the synthesis and secretion of angiogenic factors.
2. Maturation of spindle cells is associated with a decrease in gap junctions , a diminished cytoplasmic volume of rough endoplasmic reticulum and a cessation of synthesis and secretion of angiogenic factors.
3. Myofibroblasts invade the vitreous concommtantly with spindle cell maturation and provide the tractional force that can produce the retinal separation.

CRYOTHERAPY

The ablative treatment of the peripheral retina of immature infants with ROP may ameliorate the course of the disease. CRYO-ROP study was organized in 1985 under the chairmanship of Palmer. Supported by the national eye institute the study began enrolling premature infants weighing 1250 grams or less at birth in 1986.

Infants eligible for cryotherapy trial had stage 3 ROP involving 5 or more clock hours of retina posterior to zone 3 in the presence of a standardized plus disease. Contiguous non-overlapping spots of trans-scleral cryotherapy were directed at the entire anterior cuff of avascular retina.

LASER

In an effort to reduce the time and stress accompanying cryotherapy, refinements of ablative therapeutic technique were studied- in particular, laser therapy using the binocular indirect ophthalmoscope delivery system (LIO). During the early 1990s laser ablation gained acceptance as an alternative to cryotherapy. In general, ophthalmologists have found that the LIO delivery system is technically easier than cryotherapy and creates fewer postoperative sequelae related to the treatment (inflammation and swelling) than cryotherapy. Furthermore it seemed apparent that the outcomes of treatment of threshold disease in zone 1 and posterior zone 2 were superior to cryotherapy and at least equivalent to cryotherapy results for zone 2 disease.

When LIO delivery systems became available around 1990, the only laser offered was an argon photocoagulator(488-532nm). Subsequently the diode laser (810nm) photocoagulator was introduced. It has become more popular than argon because of its portability and lower incidence of postoperative cataract formation. Although circumstances may require taking patients to the operative suit for ROP laser therapy, it can also be done in the NICU, with the patient under local anesthesia, and with or without the aid or conscious sedation.

A technique of laser treatment in NICU is to place the infant swaddled in a blanket in an open warmer. Mydriatic drops are instilled an hour before beginning surgery. Treatment is performed with the aid of the infants' nurse and a neonatologist is always available in the nursery should resuscitation be necessary. A heart rate monitor, apnoea monitor, and pulsoxymeter are used throughout the procedure to alert the surgeon and nurse about any systemic problems. Topical anesthesia is instilled in the eye to be treated and then a lid speculum is placed. Lidocaine 2% is injected subconjunctivally in each quadrant(0.25-0.3cc) for local anesthesia. Approximately 10 minutes is allowed for the anesthetic to take effect. Treatment is then begun with the LIO delivery system, generally with a 28 D condensing lens for reviewing. Appropriate laser safety precautions have to taken for protection of all personnel within the line of sight of the laser beam.

Photocoagulation burns are distributed 0.5-1 burn width apart. The objective of the treatment is to scatter burns throughout the entire peripheral non-vascularised retina. This can be usually be accomplished in one treatment session. Treatment is generally started at the anterior edge of the vascularised retina and applied out to the ora serrata utilizing a swab or like instrument for eye positioning and sclera depression when

necessary to treat the peripheral retina. Initial settings for the diode laser are a power of 0.15 watts and pulse duration of 0.3-0.4 seconds. The power settings are usually sub-threshold for photo-coagulation. Power is then titrated up in increments of 50 M watts until a yellowish-grey reaction is observed in the retina. The power and pulse duration often need to be varied from one area to another in the avascular retina.

The total number of laser applications necessary to treat a given eye will depend primarily on the size of the avascular zone in the eye ; eyes with vascularisation only into zone 1 will require a larger number of laser spots than those with disease in zone 2. If the ROP is in mid to peripheral zone 2, then 600 to 1000 laser spots may be sufficient to cover the entire non-vascularised retina for 360^0. However if the eye to be treated as vessel growth only in zone 1, then it is not unusual to apply 1500-2000 laser spots for adequate coverage. Although the desire is to perform all the necessary treatment for each eye in one session, circumstances such as reduced visibility or patient distress may necessitate more than one treatment session. Occasionally, inadvertently skipped areas near the ROP ridge require supplementary treatment in 10-14 days, in the absence of signs of involution.

COMPLICATIONS OF LASER PHOTOCOAGULATION:

Like any other surgical procedure, photocoagulation may occasionally be associated with complications. the most serious complications are caused by excessive energy or misdirected light.constant attention must be paid to the foveal centre during any laser treatment to avoid hitting this vital structure,

- Inadvertent corneal burns which can lead to opacities
- Iritis
- Iris atrophy
- Papillary abnormalities due to thermal damage to the ciliary nerves in the supra choroidal space.
- Absorption by lens pigments may create lenticular burns and opacities
- Optic neuritis from treatmentdirectly to or adjacent to the disc
- Nerve fibre damage may follow intense absorbtion in zones of increased pigmentation or retinal thinning.

- Foveal burns
- Bruch’s mwmbrane ruptures,
- creationa of retinal or choroidal lesions like tear or hole.
- Exudative retinal detachment
- Rhegmatogenous retinal detachment.

Accidental foveal burns:

Great care must be taken to identify fovea . frequent reference to foveal centre throughout the session is helpful to avoid losing track of where in the fundus the treatment is taking place.

Bruch’s membrane ruptures:

Small spot size, high intensity , and long duration of applications all increase the risk of a Bruch’s membrane rupture , which may subsequently give rise to hemorrhage from choriocapillaries.

CICATRICIAL DISEASE:

About 20% of infants with active ROP develop cicatricial complications, which range from innocuous to extremely severe. In general, the more advanced or the more posterior the proliferative disease is at the time of involution, the worse the cicatricial sequelae.

STAGE 1:

Peripheral retinal pigmentary disturbance and haze at the vitreous base.

STAGE 2:

Temporal vitreo-retinal fibrosis and straightening of vascular arcades followed by dragging of the macula and disc occurs in this stage. This may lead to a pseudo- exotropia due to resultant exaggeration of angle kappa.

STAGE 3:

More severe peripheral fibrosis with contracture and falciform retinal fold is seen.

STAGE 4:

Partial ring of retrolental fibro-vascular tissue with partial retinal detachment may occur.

STAGE 5:

Complete ring of retrolental fibro vascular tissue with total retinal detachment occurs. This stage was formerly called as retrolental fibroplasia.

Part Two

A STUDY ON CLINICAL OUTCOMES OF LASER PHOTOCOAGULATION FOR PREMATURE RETINOPATHY

AIM

To study the outcomes of laser photocoagulation for premature retinopathy.

PRIMARY OBJECTIVE:

- To analyze the outcomes of laser photocoagulation in retinopathy of prematurity.

SECONDARY OBJECTIVE:

- Prevention of complications of retinopathy of prematurity by arresting disease process at an earlier stage.
- Assessing the percentage of occurrence of various stages of ROP.

INCLUSION CRITERIA (BASED ON INTERNATIONAL CLASSIFICATION OF ROP):

- Birth weight <1500g .
- <32 weeks of gestational age.

EXCLUSION CRITERIA:

- Babies with birth weight more than 1500 gram.
- Infants with gestational age more than 32 weeks.

MATERIALS AND METHODS

Sick preterm babies treated for respiratory distress syndrome / pneumonitis by supplementary oxygen were screened.

Other co-morbid conditions such as neonatal hyper-bilirubinemia treated by phototherapy or multiple blood transfusions were included in the study.

Registration:

Registration was done with an ROP screening number using the proforma.

Details of gestational age, post-conceptional age, birth weight, post natal age were noted in the ROP screening proforma.(figure 1).

Screening conditions:

Examination of the infants was conducted in ROP screening cubicle.

A/C and fan are avoided to prevent hypothermia. Babies were wrapped adequately with a sterile cloth which facilitates examination by restricting movements of the baby as well as providing warmth to the baby.

Care was taken not to disturb the external mileusis of the baby who are in intensive care unit under artificial ventilator supports. (figure 2)

Aseptic precautions were undertaken like washing hands, wearing cap and mask. Sterilized pediatric wire speculum and sclera indenters were used for fundus examination.

Screening process:

- The infants satisfying the inclusion criteria are registered.
- Anterior segment examination is done to rule out hazy cornea, shallow anterior chamber, rigid pupil, leukocoria.
- Pupil is dilated with 0.25% tropicamide and 0.5% phenylephrine.
- 0.5% paracaine is used as topical anesthetic.
- Fundus evaluation is done using indirect ophthalmoscope and 20D convex lens.
- Pediatric speculum and scleral indenter are used to view the retinal periphery.
- The findings are recorded in the screening register with diagrams and plan of management.
- Infants with threshold ROP or higher stage are planned for laser photocoagulation.

Staging of ROP:

- Stage 1 – demarcation line between the perfused and non-perfused retina
- Stage 2 – ridge formation between the perfused and non-perfused retina as the demarcation line acquires a height and width
- Stage 3 – extra retinal fibro vascular proliferation occurs at the site of ridge (figure 3).
- Stage 4 – subtotal Retinal Detachment
  - Stage 4A does not involve the fovea.
  - Stage 4B involves the fovea.
- Stage 5 - total retinal detachment.
  - Stage 5A is an open funnel.
  - Stage 5B is a closed funnel.

TREATMENT PROTOCOL (ETROP - EARLY TREATMENT ROP):

- ETROP type 1 – zone 1, any stage, plus

  Or stage 3 without plus,

  Zone 2, stage 2 or 3,

  With plus (Pre-threshold).

Figure 4 shows plus disease (venous tortuosity in the posterior pole).

Figure 5 shows stage 3 in zone 2 of the same child (extra retinal fibro vascular proliferation).

OBSERVATION AND ANALYSIS

LASER INDIRECT OPHTHALMOSCOPY:

The pupils are dilated with 0.25% tropicamide and 0.5% phenylephrine. 0.5% paracaine is applied topically to anaesthetize the eye. The infant is monitored with a pulsoxymeter by a neonatologist.

Photocoagulation of peripheral retina is done using a frequency doubled Neodymium- YAG laser of wavelength 532nm by indirect ophthalmoscope. Antibiotic and anti inflammatory eye drops are given 4 times a day for 1 week following laser. Figure 6 shows post laser fundus picture of the stage 3 plus disease.

The total number of laser applications necessary to treat a given eye will depend primarily on the size of the avascular zone in the eye ; eyes with vascularisation only into zone 1 will require a larger number of laser spots than those with disease in zone 2. If the ROP is in mid to peripheral zone 2, then 600 to 1000 laser spots may be sufficient to cover the entire non-vascularised retina for 360^0. However if the eye to be treated as vessel growth only in zone 1, then it is not unusual to apply 1500-2000 laser spots for adequate coverage. Although the desire is to perform all the necessary treatment for each eye in one session,

circumstances such as reduced visibility or patient distress may necessitate more than one treatment session. Occasionally, inadvertently skipped areas near the ROP ridge require supplementary treatment in 10-14 days, in the absence of signs of involution.

THE ETROP RECOMMENDATIONS FOR FOLLOW UP:

Twice a week if there is type 2 ROP

- Zone 2, no plus, stage 3 (or with plus, stage 1)
- Zone 1 , no plus,stage 1 or 2

Every week if the ROP is near type 2

- Zone 2 , no plus, stage 2
- Zone 1 , immature , no ROP

Every 2 weeks if less concerning

- Zone 2 , no plus, immature or stage 1

Favourable signs with respect to progression or involution of ROP include attainment of post-menstrual age of 45 years without developing atleast type 2 ROP and either the completion of full retinal vascularisation or progression of retinal vascularisation into zone 3 without previous zone 2 ROP.

Until ROP can be prevented, it behooves us, the physicians caring for the premature infants to detect cases that need treatment through co-ordinate and timely methods in order to benefit each of our recovering pre-term patients.

Neonatologists, ophthalmologists discharge coordinators and ROP coordinators must collaborate in adhering to local policies that are developed for the benefit of theses infants.

RESULTS

Totally 202 babies were screened in a duration of two years. The mean gestational age of babies screened was 30.25 weeks and the mean birth weight was 1.25 Kg. out of the 202 babies screened, 73 babies had ROP. Three pairs of twins were also affected by ROP among others. Out of the 73 ROP babies 17 required laser treatment. 14 of those who were treated with laser recovered whereas 3 babies progressed to retinal detachment, most probably due to late stage of presentation. The probability value was found to be 0.008 which is significant.

No. of babies examined	:	202
Mean gestational age	:	30.25 wks
Mean birth weight	:	1.25 kg
No. of babies diagnosed to have ROP -	:	73
No. of twins diagnosed to have ROP	:	3
No. of babies who were given laser	:	17
No. of babies with regressed ROP following laser	:	14
No. of babies who progressed to RD even after laser	:	3

DISCUSSION

From the data collected, it is found that out of the 202 babies screened, 73 babies had ROP. Out of the 73 ROP babies, 17 required laser photocoagulation, out of which 14 responded very well, but 3 did not respond.

According to Chi-square test,

$X^2 = 7.11$

P = 0.008

The P value is significant

The three babies which progressed to total retinal detachment had been brought for screening only in the late stages, that is, in stage 4 with or without plus disease. This shows that, early diagnosis and management is the mainstay of treatment of retinopathy of prematurity.

Parents' education regarding the importance of periodic follow up is very important.

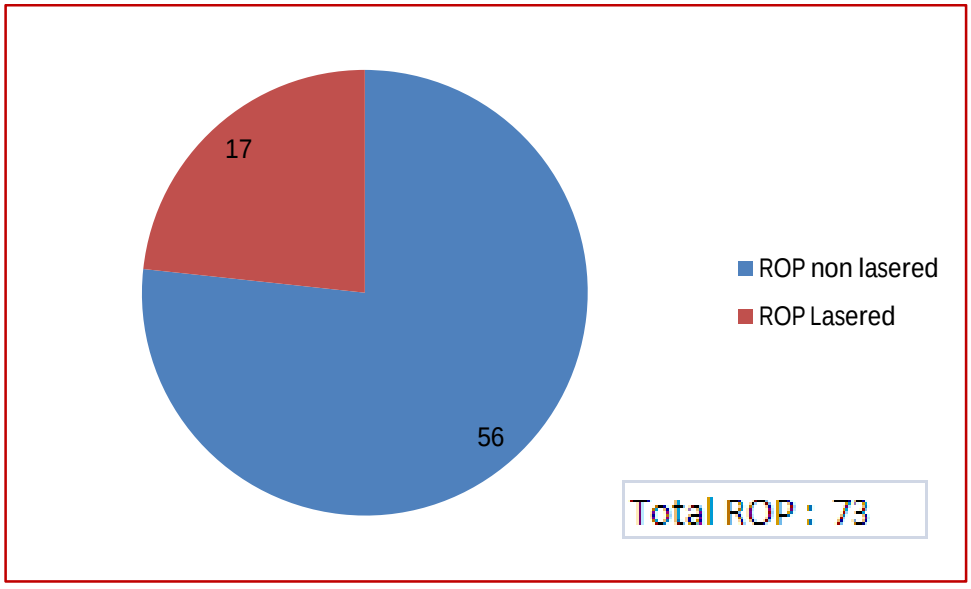
Surgical management for stage 5 has poor prognosis.

Majority of the babies affected by ROP were male. Regular screening helps detect ROP in an early stage as shown in the chart depicting the percentage of occurrence of various stages of ROP Intra-vitreal anti-vascular endothelial growth factor can be given but visual prognosis is not as good as that following laser photocoagulation.

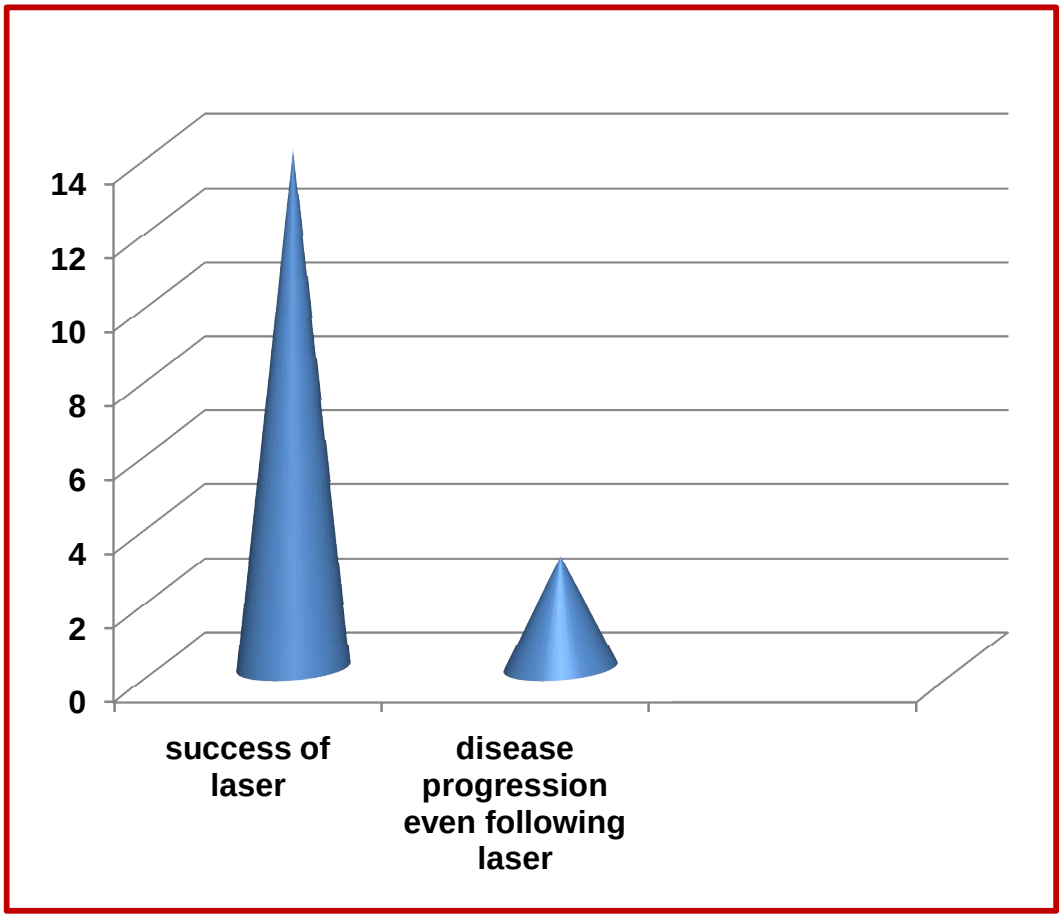
Birth asphyxia is one the major risk factor in the development of ROP.

Out of 73 babies diagnosed to have ROP, 17 required laser of which 14 recovered. This shows the better visual outcome following laser.

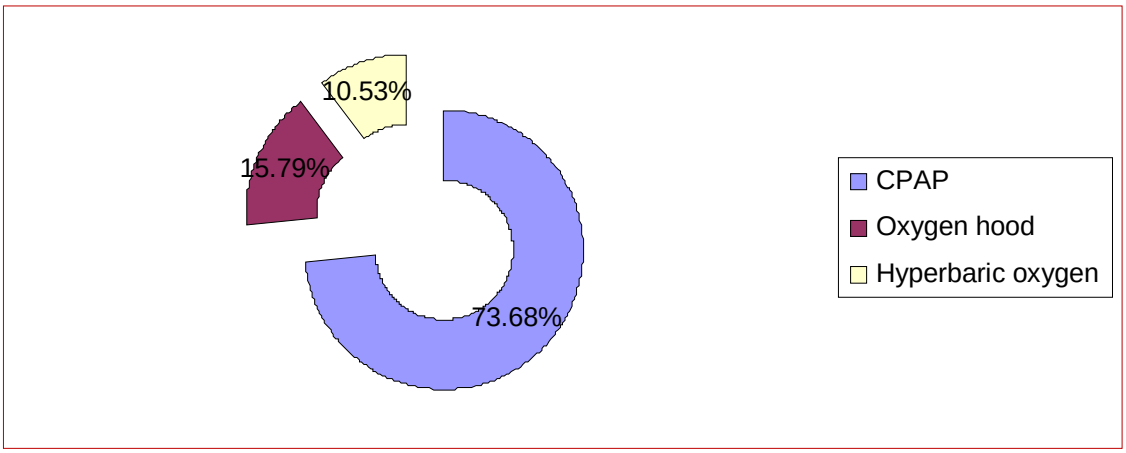
CHART SHOWING THE NUMBER OF ROP BABIES REQUIRING LASER



SUCCESS OF LASER IN ROP



Percentage chart showing the significance of positive pressure ventilation in the occurrence of ROP:



Sex Predilection:

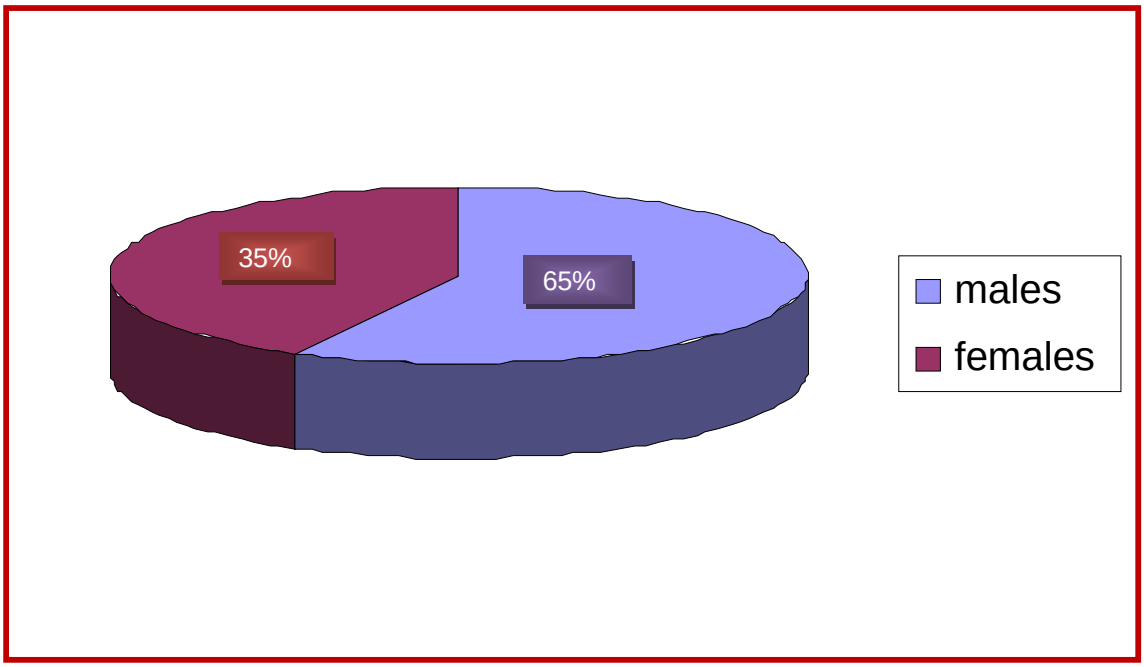
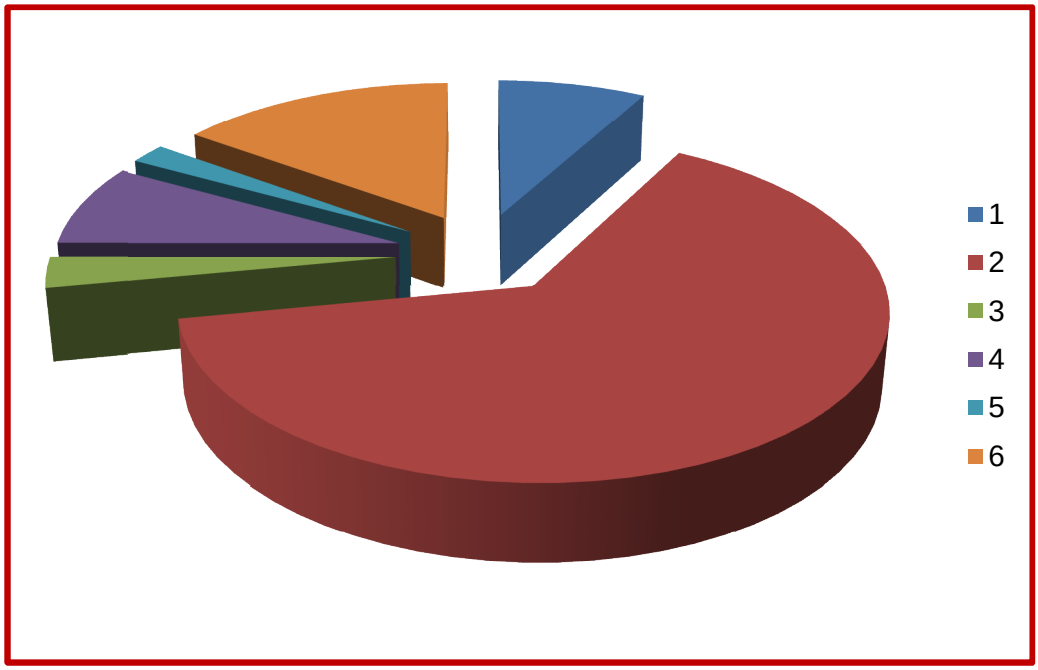
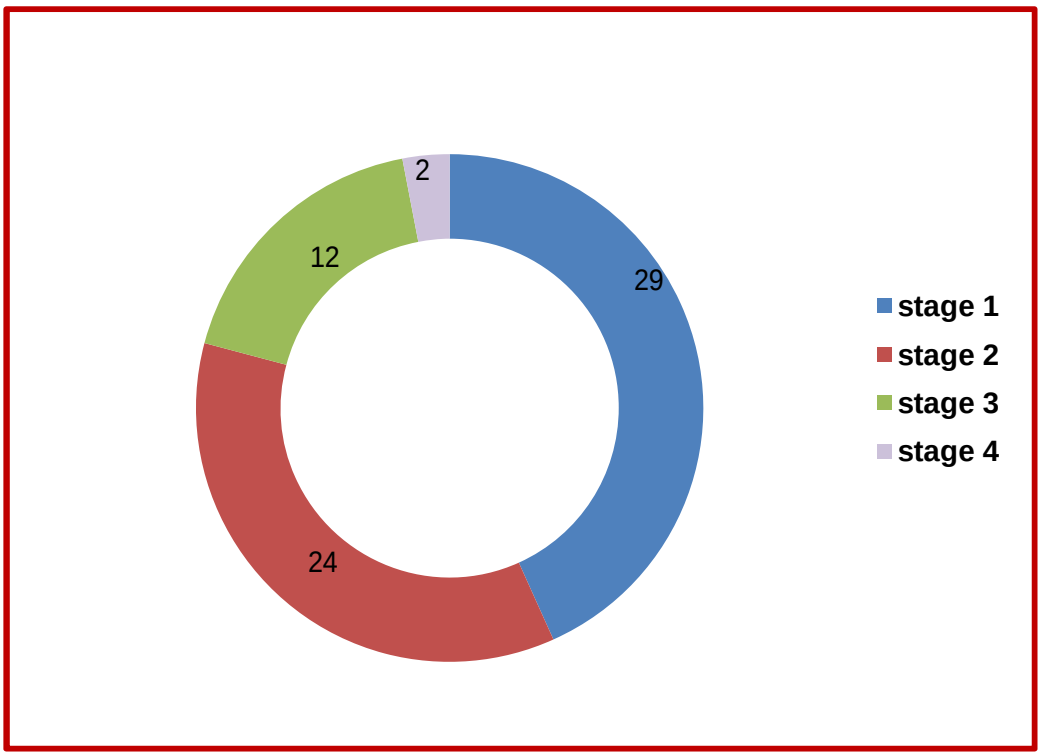


Chart showing the various co morbid condition associated with ROP:



1. Neonatal hyperbilirubinemia 6%
2. Birth asphyxia 64%
3. Seizures7%
4. Neonatal septicemia 5%
5. Pneumonitis 2%
6. Respiratory distress syndrome 16%

Chart showing the relative occurrence of various stages of ROP



MATURITY OF RETINA VS GESTATIONAL AGE

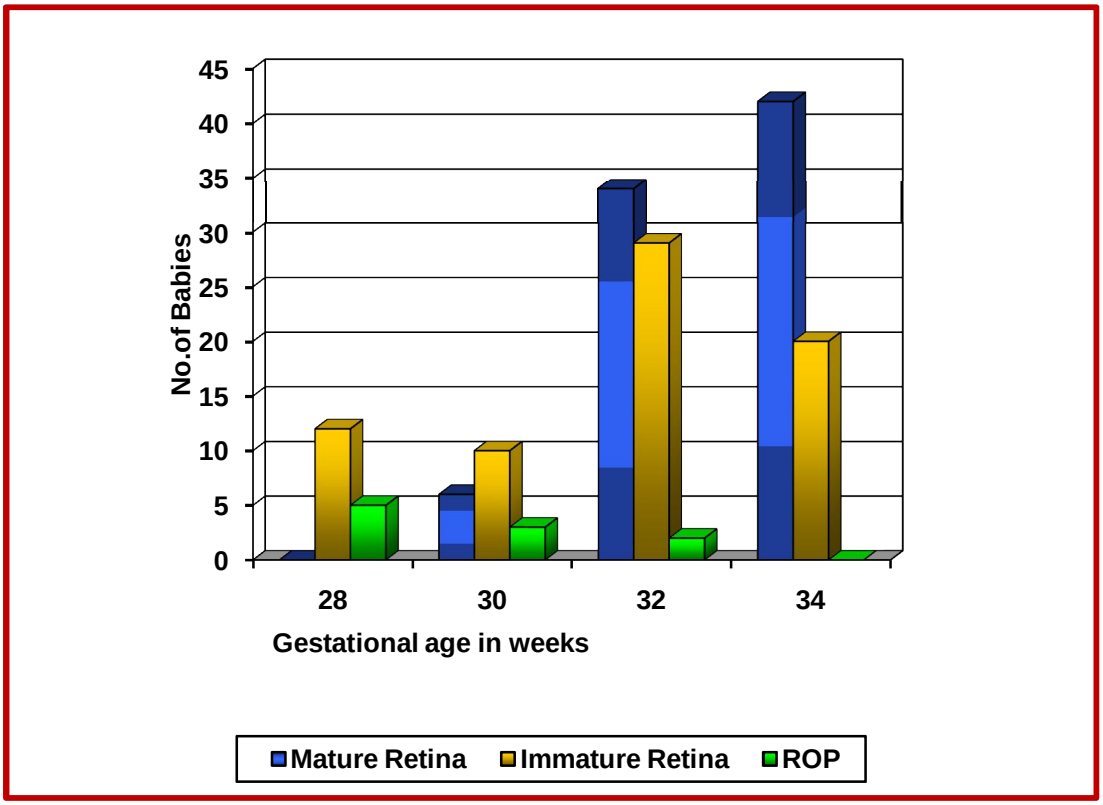
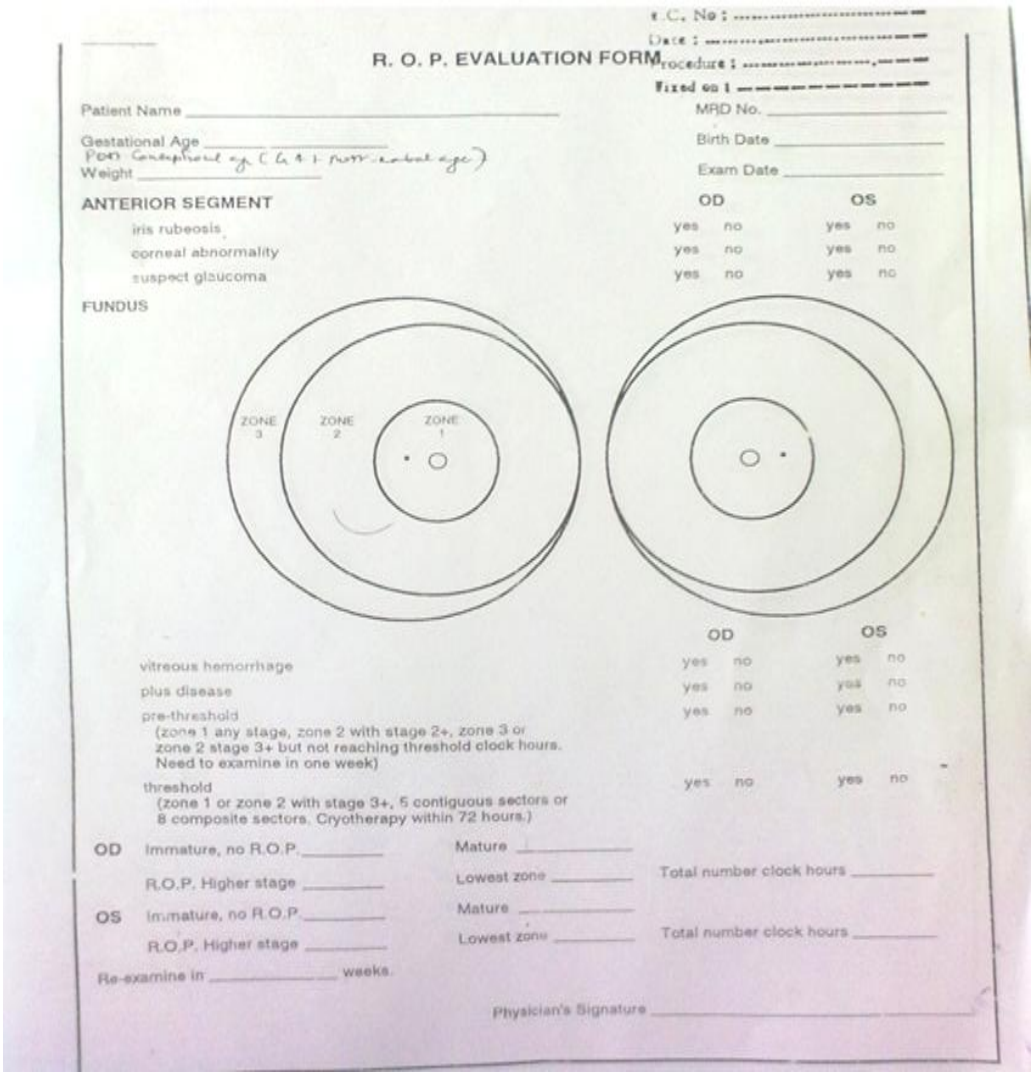


Figure 1:

ROP evaluation form



R. O. P. EVALUATION FORM

Patient Name _____ MRD No. _____

Gestational Age _____ Birth Date _____

(Post Conceptional age (G.A + post natal age))

Weight _____ Exam Date _____

ANTERIOR SEGMENT

	OD		OS	
iris rubeosis	yes	no	yes	no
corneal abnormality	yes	no	yes	no
suspect glaucoma	yes	no	yes	no

FUNDUS

ZONE 3 ZONE 2 ZONE 1

	OD		OS	
vitreous hemorrhage	yes	no	yes	no
plus disease	yes	no	yes	no
pre-threshold (zone 1 any stage, zone 2 with stage 2+, zone 3 or zone 2 stage 3+ but not reaching threshold clock hours. Need to examine in one week)	yes	no	yes	no
threshold (zone 1 or zone 2 with stage 3+, 5 contiguous sectors or 8 composite sectors. Cryotherapy within 72 hours.)	yes	no	yes	no

OD Immature, no R.O.P. _____ Mature _____

R.O.P. Higher stage _____ Lowest zone _____ Total number clock hours _____

OS Immature, no R.O.P. _____ Mature _____

R.O.P. Higher stage _____ Lowest zone _____ Total number clock hours _____

Re-examine in _____ weeks.

Physician's Signature _____

Figure 2:

ROP baby with ventilator support in a neonatal intensive care unit

Figure 3:

Zones of Involvement of ROP

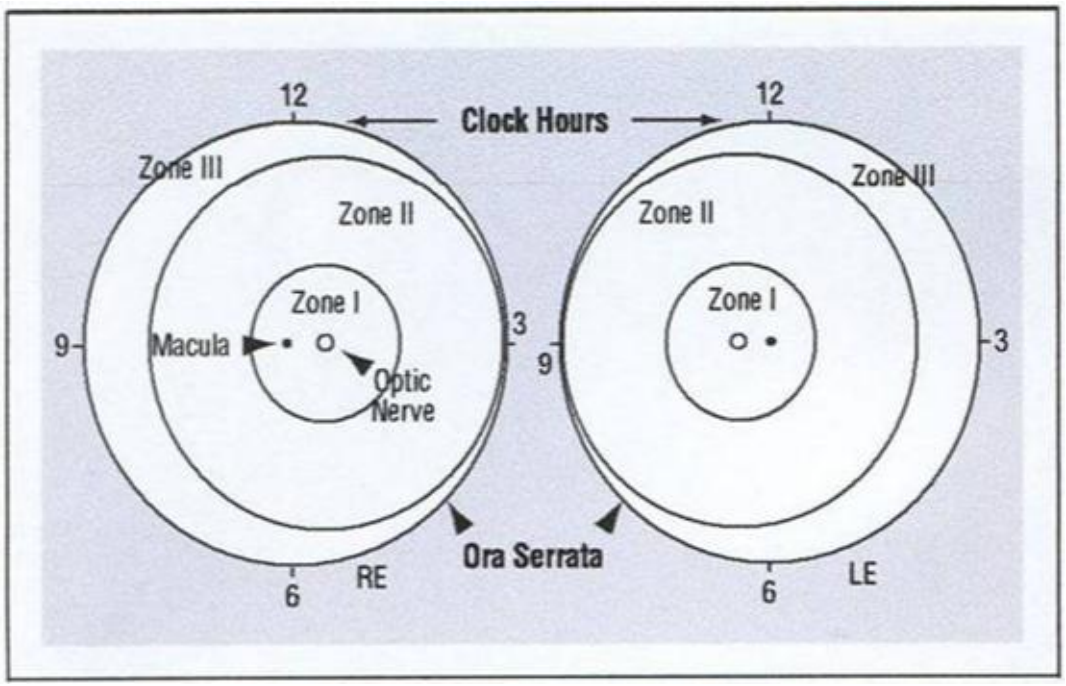


Figure 4:

Plus disease

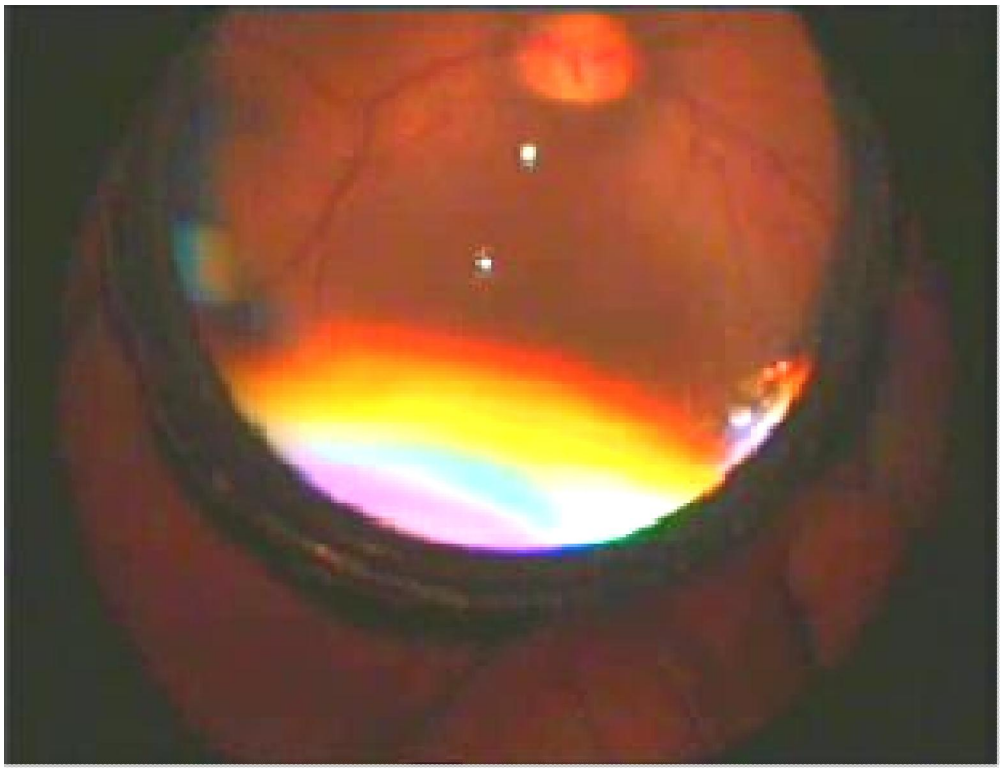


Figure 5:

Extra retinal fibro-vascular proliferation – stage 3 in zone 2

Figure 6:

Post laser status showing regressed ROP

Figure 7:

Peadiatric speculum for better exposure

Figure 8:

Tortuos vessels in the posterior pole

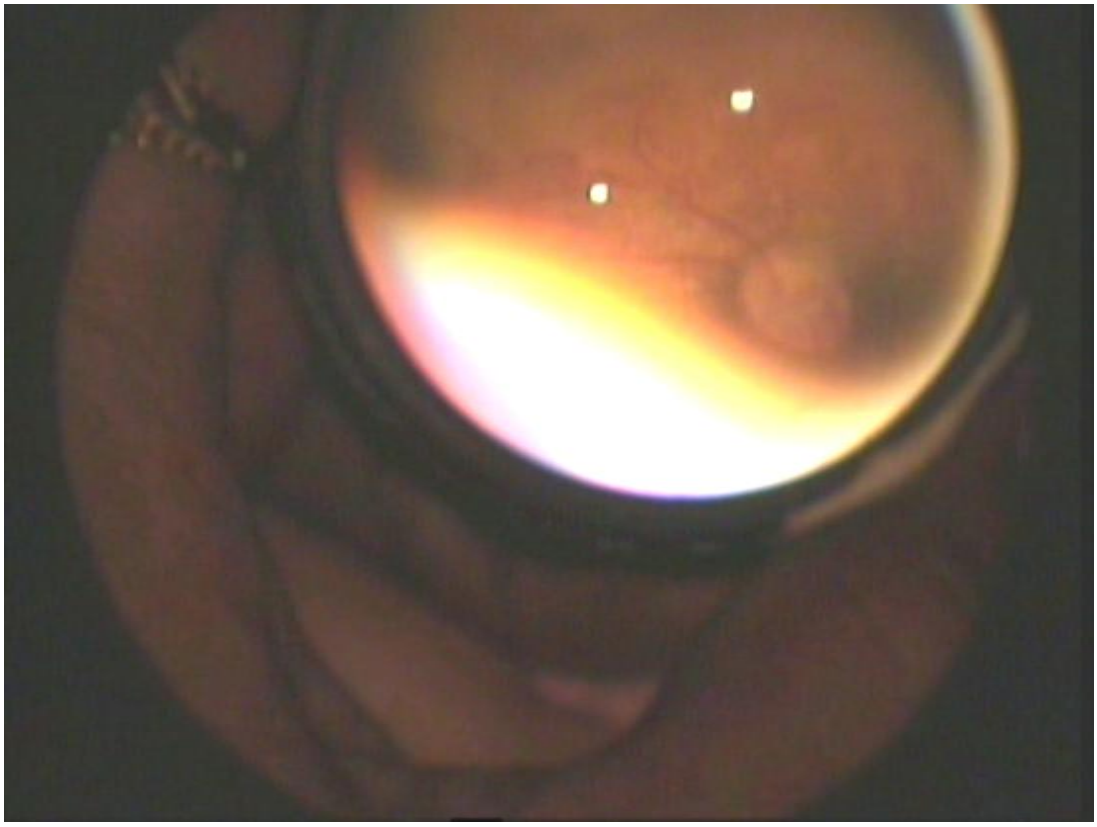


Figure 9:

Popcorn neovascularisation

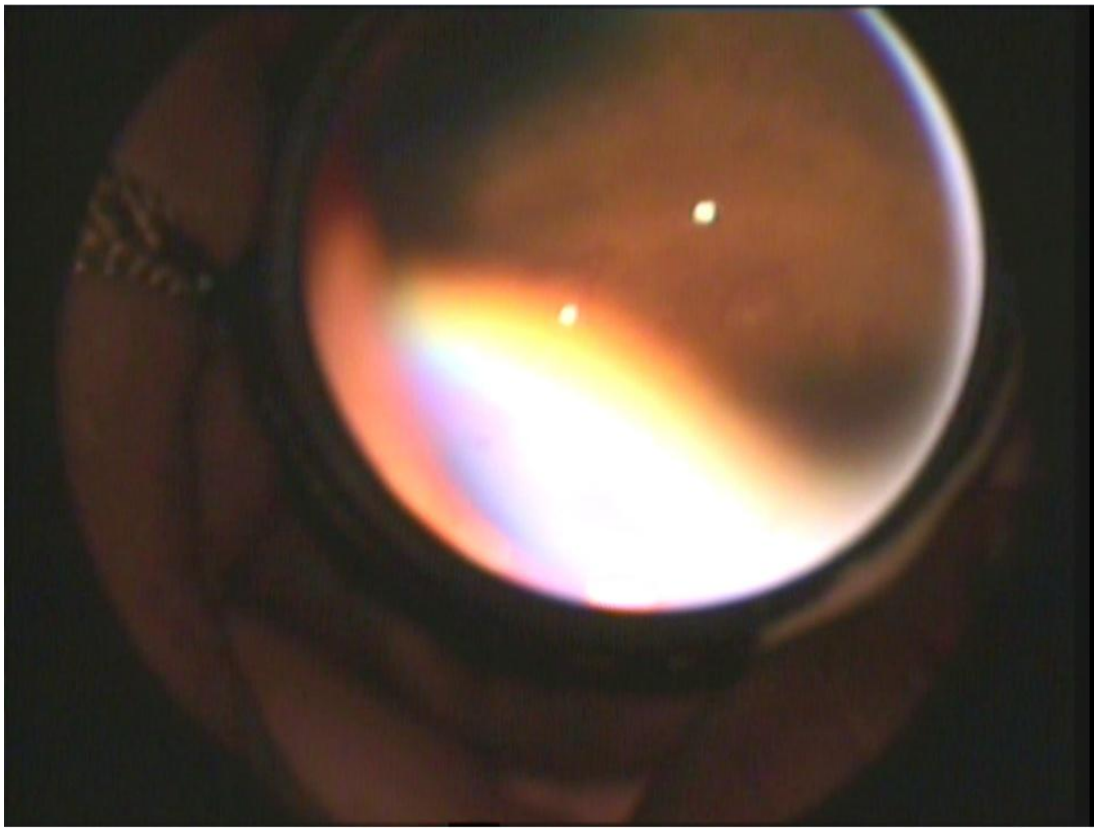


Figure 10 :

Pre-retinal hemorrhages in zone 3

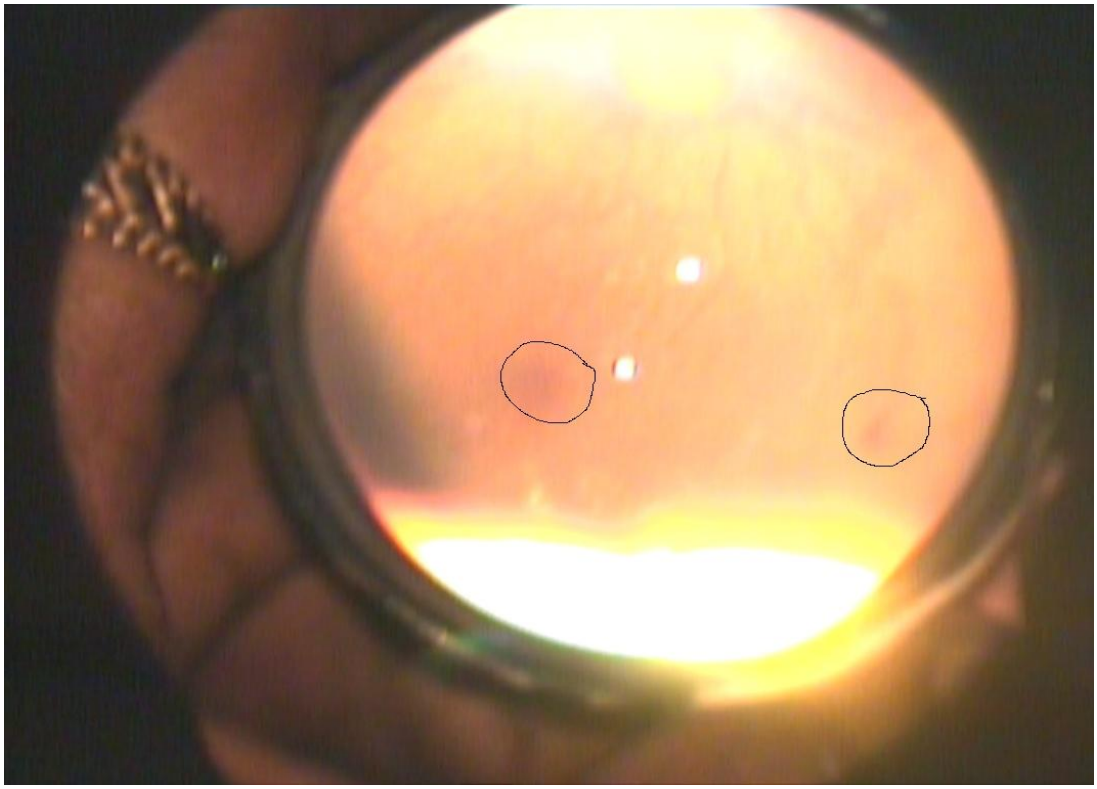


Figure 11:

Regressed ROP following laser burns in the periphery seen as dark spots

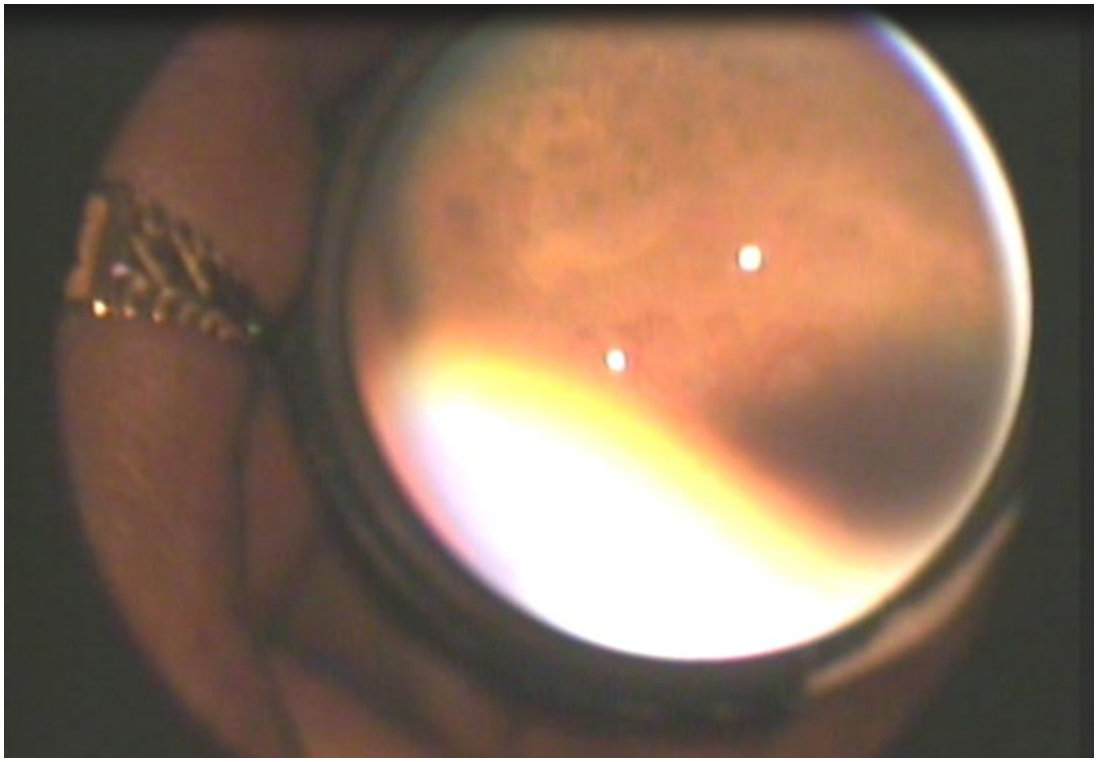


Figure 12:

New vessels in zone 2 infero-temporally with plus disease

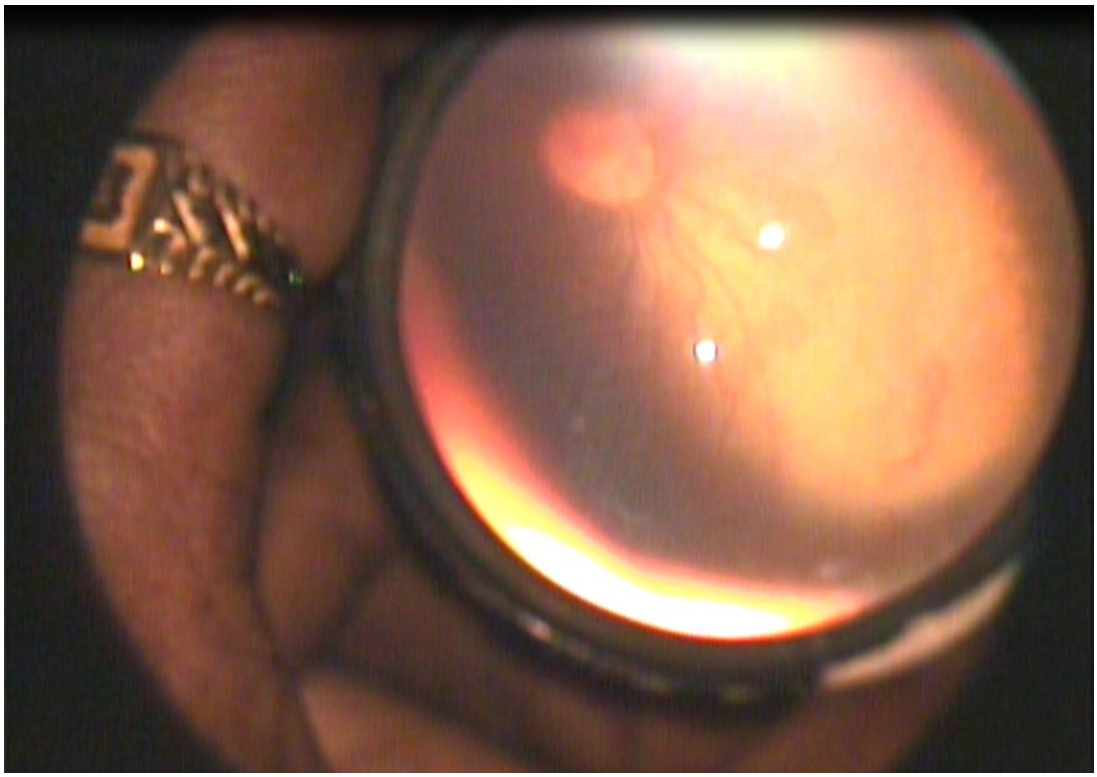


Figure 13:

Scleral indentation to view the periphery of retina

Figure 14:

Frequent application of lubricating eye drops to prevent dryness of cornea.

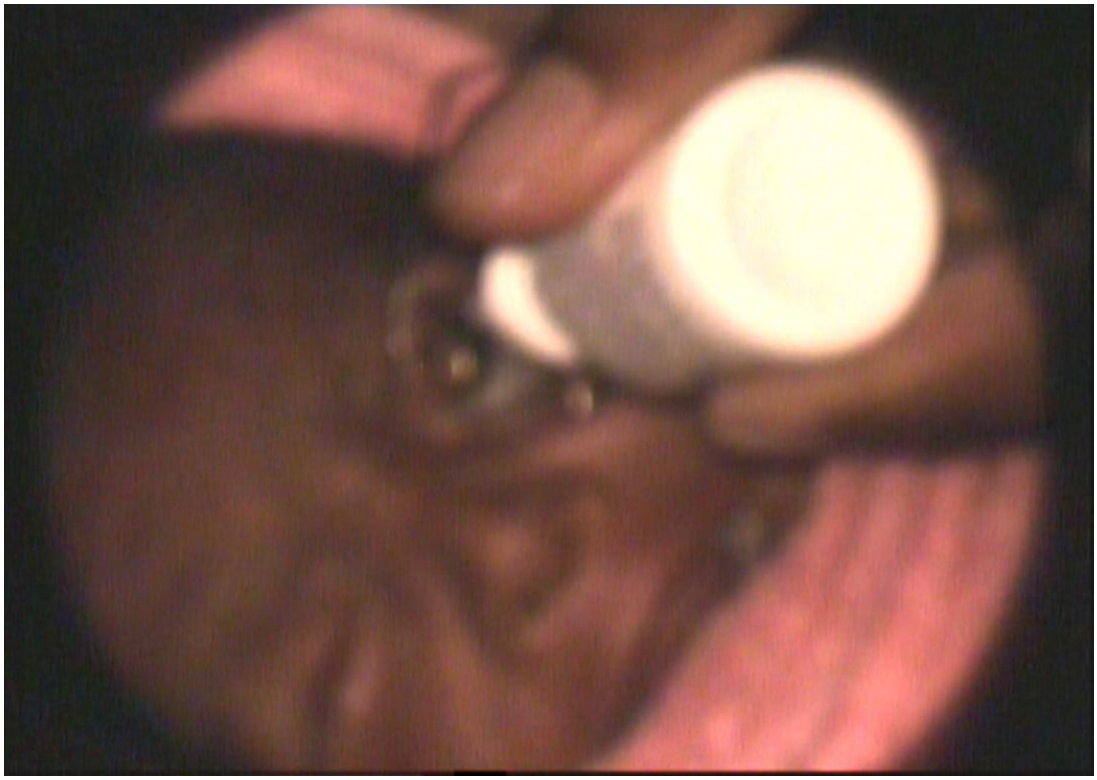


Figure 15:

Regressed vascular fronts following laser

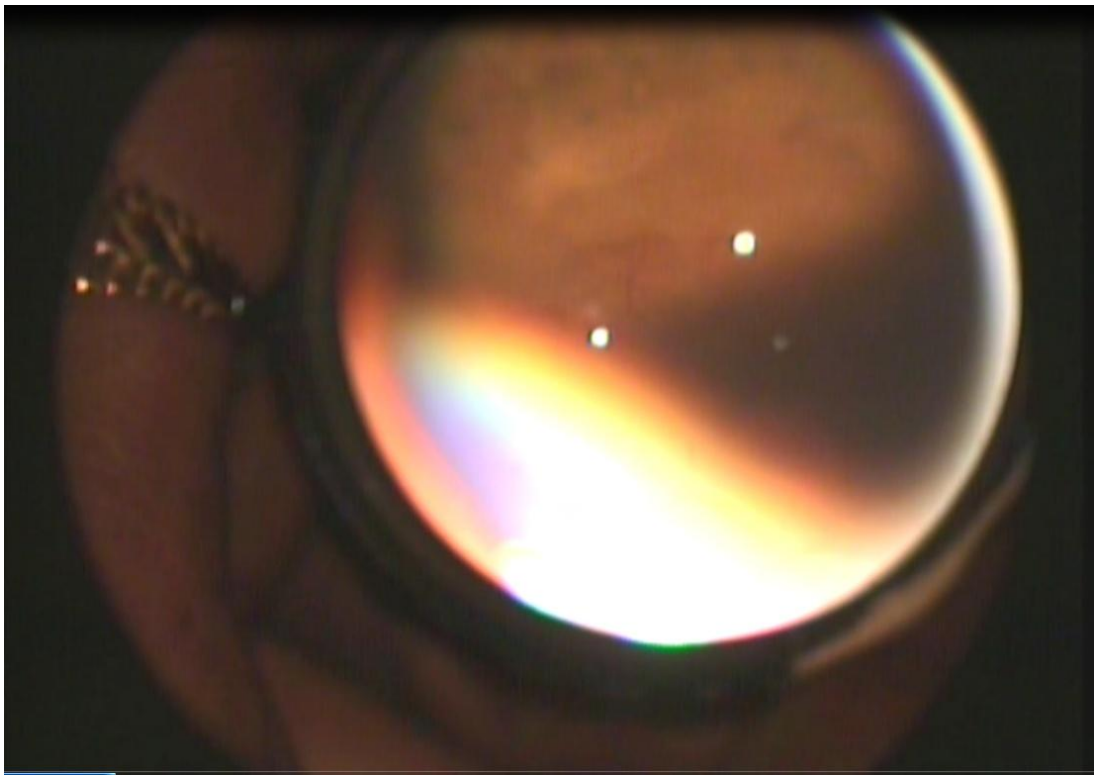


Figure 16:

Well dilated pupil for adequate photocoagulation of the periphery

Figure 17:

Premature babies undergoing phototherapy for neonatal hyperbilirubinemia which is one of the risk factor for ROP

The pictures depict the various observations during the examinations and laser photo coagulation therapy. The explanation to the pictures is as follows. Risk of hypothermia is predominant in premature and pre term infants. Wrapping up the baby is very essential to avoid the risk of hypothermia in premature or preterm infants. Most of them would be on phototherapy for hyper-bilirubinemia as shown in figure 17. Hence maintenance of thermal equilibrium is important.

The limbs and the body are covered as shown in figure 13. This is called mummification. For adequate exposure of the peripheral retina, a well dilated pupil is needed as shown in figure 16. Pediatric speculum and sclera indentation helps the examiner to view all the zones of retina as shown in figure 13.

Figure 8 shows the posterior pole with tortuous vessels suggestive of plus disease.

Figure 12 shows neovascularisation in zone 2 associated with tortuous vessels in the posterior pole. Figure shows the post laser status of the same baby with regressed ROP. The laser burns are seen as hyper pigmented spots in the periphery.

Figure 12 shows new vessels at the junction of perfused and non-perfused retina. Figure 10 shows pre-retinal hemorrhages marked in black circles. These are suggestive of leak from the new abnormal

vessels. Figure 11 shows the post laser status of the baby with stage 3 with plus disease. The laser marks are visible as dark spots in the periphery.

Frequent application of tear substitutes is essential to prevent dryness of cornea both during examination by indirect ophthalmoscope as well as during laser as shown in figure 14.

CONCLUSION

Retinopathy of prematurity is a potentially blinding disorder which can be prevented from progressing to blindness if timely screening is undertaken. Premature/ pre-term babies and babies at increased risk such as birth asphyxia, respiratory distress syndrome, hyper-bilirubinemia, positive pressure ventilation etc need to be followed up according to the Early Treatment of ROP study. Pre-threshold/threshold ROP needs immediate intervention with laser. Following laser, periodic follow up needs to be done to look for the response. If not responding, then further sittings of laser need to be given.

The prognosis following laser in the threshold / pre-threshold stage is very good. From the study it is found that 14 out of 17 babies responded very well. 9 babies responded with a single sitting of laser itself. 2 babies who were not brought for screening by the parents earlier were diagnosed to have stage 3 ROP in zone 1 with plus disease, did not respond to laser and progressed to stage 4. They were referred to centers where surgeries for retinal detachment and anti vascular endothelial growth factor were given but the retinal detachment persisted.

This shows that early and periodic screening is the mainstay in early detection and management which influences the outcome and visual prognosis.

The babies are followed up till 42 weeks post-conceptional age or till retina matures completely.

Regular follow up till age 12 years is required to correct refractory errors or diagnose late complications like cataract, strabismus, tractional RD, high myopia, secondary open angle glaucoma.

Prevalence of ROP was found to be 18.8% as against 23.27%, according to the study conducted in AIIMS in the year 2010.

There is male preponderance. Twins are invariably affected probably due to low birth weight, hyperbilirubinemia and positive pressure ventilation in them. Among the risk factors evaluated birth asphyxia was found to have a higher risk of developing ROP. Regular screening would help in detecting early ROP in stage 1 which would help prevent progression to higher stages which would lead to blindness if not treated at the right time.

73.33% of the babies who were given laser were followed for 6 month and found to have regressed ROP. The follow will be continued annually till 12 years to correct the refractory errors and prevent amblyopia.

Part Three

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PROFORMA

Name:

ROP registration number:

Gestational age:

Post conceptional age:

Birth weight:

MRD number:

Birth date:

Examination date:

Birth history:

History of supplementary oxygen:

ANTERIOR SEGMENT:

Rubeosis iridis:

Corneal abnormality:

Glaucoma:

FUNDUS DIAGRAM:

Vitreous hemorrhage:

Plus disease:

Pre-threshold:

Threshold:

DIAGNOSIS: OD /OS

Threshold/ pre-threshold/no ROP

Number of clock hours involved _____

Re-examine in _____ weeks.

30. Physician’s signature:

Master Chart

MASTER CHART

SERIAL NO:	ROP REGISTRATION NUMBER	BIRTH WEIGHT	GESTATIONAL AGE	POST-CONCEPTIONAL AGE	DIAGNOSIS	TREATMENT/ FOLLOW UP	OUTCOME
1	161/11	1.3	32	45	BE zone 3 stage 2	Biweekly follow up	Regressed
2	183/11	1.2	31	37	BE zone 3 stage 3	Weekly follow up	Regressed
3	186/11	1.2	30	36	BE zone 3 stage 2	Biweekly follow up	Regressed
4	160/11	1.15	32	46	RE stage 1 zone 3 LE NAD	Biweekly follow up	Regressed
5	161/11	1.3	32	46	BE zone 3 stage 2	Biweekly follow up	Regressed
6	189/11	1.5	32	37	BE stage 2 zone 3	Biweekly follow up	Regressed
7	191/11	1.33	34	37	BE stage 2 zone 3	Biweekly follow up	Regressed
8	196/11	1.7	32	38	BE regressed ROP	Monthly follow up	Regressed
9	197/11	1.04	33	37	RE stage 2 zone 3	Biweekly follow up	Regressed
10	141/11	1.8	28	43	BE regressed ROP	Monthly follow up	Regressed
11	188/11	1.2	30	39	RE stage 2 zone 2 3 clock hours	Biweekly follow up	Regressed
12	185/10	1	28	32	BE stage 2 zone 3	Biweekly follow up	Regressed
13	208/11	1.3	28	33	BE stage 2 zone 3	Biweekly follow up	Regressed
14	213/11	1	29	35	BE stage 1 zone 3	Biweekly follow up	Regressed

SERIAL NO:	ROP REGISTRATION NUMBER	BIRTH WEIGHT	GESTATIONAL AGE	POST-CONCEPTIONAL AGE	DIAGNOSIS	TREATMENT/ FOLLOW UP	OUTCOME
15	221/11	1.25	33	40	BE stage 1 zone 3	Biweekly follow up	Regressed
16	212/11	1.1	28	34	BE stage 1 zone 3	Biweekly follow up	Regressed
17	225/11	1.4	30	38	BE stage 3-4 zone 3	PRP 2 sittings	regressed
18	213/11	1	32	36	Zone 2 stage 3	Laser 1 sitting	regressed
19	245/11	1.25	34	40	BE zone 3 stage 1	Biweekly follow up	Regressed
20	246/11	1.2	28	32	BE stage 1 zone 2	Biweekly follow up	Progressed to plus disease, hence laser given, regressed
21	251/11	1.3	28	34	RE zone 3 stage 1, LE zone 2 stage 2	Biweekly follow up	Regressed
22	256/11	1.36	31	36	BE stage 2, zone 2 , plus disease	laser	regressed
23	254/11	1.22	29	36	BE stage 2 , zone 3	Biweekly follow up	Regressed
24	262/11	1.25	30	34	RE stage 2, zone 2, plus, LE stage 3, zone 2 plus	2 sittings laser	Developed NVE RE, LE regressed ROP,2nd sitting laser given for RE

SERIAL NO:	ROP REGISTRATION NUMBER	BIRTH WEIGHT	GESTATIONAL AGE	POST-CONCEPTIONAL AGE	DIAGNOSIS	TREATMENT/ FOLLOW UP	OUTCOME
25	262/11	1.25	30	37	NVE persistent inferiorly	3rd sitting laser	BE regressed
26	258/11	700gm	26	31.5	Stage 1 zone 3 BE	Biweekly follow up	Regressed
27	269/12	1.3	30	34	BE stage 1 zone 2 with plus	2 sittings laser	Regressed
28	272/12	1.25	32	36	Plus disease	1 sitting laser	Regressed
29	279/12	1.6	36	40	Stage 1 , zone 2	Biweekly follow up	Regressed
30	288/11	920gm	24	28	Stage 2 , zone 2 with plus disease	PRP BE	Regressed
31	292/11	1	30	42	BE stage 4b,cryopexy and PRP BE done in a private hospital	Biweekly follow up	Persistent RD
32	293/11	1.75	36	38	Stage 3 zone 2 with plus BE	PRP BE	Regressed
33	209/11	1.48	28	31	Stage 1, zone 3	Biweekly follow up	Regressed
34	283/12	1.5	36	50	Stage 2 , zone 3	Biweekly follow up	Regressed
35	305/12	850gm	28	36	RE stage 2 zone 1 in 3 clock hours	Biweekly follow up	Regressed
36	03/10	677gm	28	32	Be plus disease	BE PRP	Regressed

SERIAL NO:	ROP REGISTRATION NUMBER	BIRTH WEIGHT	GESTATIONAL AGE	POST-CONCEPTIONAL AGE	DIAGNOSIS	TREATMENT/ FOLLOW UP	OUTCOME
37	20/10	1.29	28	33	BE stage 3 zone2	Biweekly follow up	Regressed
38	46/10	1.08	28	34	BE stage 3 zone 2	2 sittings PRP	Regressed
39	56/10	1.02	30	38	BE stage 4A Post laser , post macugen status	Weekly follow up	Persistent stage 4a
40	85/10	980 gm	30	34	RE stage 3 plus disease LE stage 2 zone 2 plus	2 sittings PRP	No response
41	89/10	1.40	32	36	RE zone 3 stage 1, LE zone 3 immature	Biweekly follow up	Regressed
42	91/10	1.33	32	40	RE zone 3 stage 2,LE zone 3 stage 1	Biweekly follow up	Regressed
43	92/10	1.14	32	40	RE zone 3 stage 1,LE immature	Biweekly follow up	Regressed
44	74/10	1.5	32	42	BE stage 1 zone 3	Biweekly follow up	Regressed
45	98/10	960gm	28	34	BE spontaneously regressed zone 3 stage 3	Monthly follow up	Regressed

SERIAL NO:	ROP REGISTRATION NUMBER	BIRTH WEIGHT	GESTATIONAL AGE	POST-CONCEPTIONAL AGE	DIAGNOSIS	TREATMENT/ FOLLOW UP	OUTCOME
46	99/10	1.09	28	31	RE zone 3 immature, LE stage 1 zone 2	Biweekly follow up	Regressed
47	103/10	2	32	40	LE resolved ROP, RE immature	Monthly follow up	Regressed
48	112/10	1.14	31	36	BE aggressive posterior ROP with NVE	Laser, 2 sittings	Regressed
49	116/10	1.016	30	37	RE stage 2 zone 3, stage 3 zone 2, LE stage3 zone 3	Weekly follow up	Regressed
50	123/10	1.65	34	43	RE regressing stage 3 2 clock hours, LE stage 3 ,mild plus, pre-threshold	Laser, 3 sittings	Regressed
51	131/10	1.8	32	40	RE stage 1 zone 2, LE immature retina	Biweekly follow up	Regressed
52	126/10	1.78	28	35	RE stage 2, 4-5 clock hours, pre-threshold LE stage 2- 5 clock hours	laser	Regressed
53	131/10	1.2	30	36	BE stage 1 zone 2	Biweekly follow up	Regressed
54	62/10	1.38	51	31	BE regressed ROP stage 2 zone 3,		Regressed

SERIAL NO:	ROP REGISTRATION NUMBER	BIRTH WEIGHT	GESTATIONAL AGE	POST-CONCEPTIONAL AGE	DIAGNOSIS	TREATMENT/ FOLLOW UP	OUTCOME
55	133/10	1.1	29	33	RE stage 1 zone 3, LE stage 1 zone 3 5 clock hours	Biweekly follow up	Regressed
56	120/10	1.2	28	38	LE stage 1RE stage 2	Biweekly follow up	Regressed
57	121/10	900gm	32	44	RE stage 2 regressed ROP, LE temporal retina immature	Biweekly follow up	Regressed
58	137/10	1.14	29	34	LE stage 1	Biweekly follow up	Regressed
59	134/10	1.45	31	35	RE zone 3 stage 1,LE immature	Biweekly follow up	Regressed
60	150/11	1.14	29	38	RE stage 1 3clock hours, LE stage 1	Biweekly follow up	Regressed
61	152/11	1.3	31	35	RE stage 3 zone 3, LE stage 3 zone 2	Biweekly follow up	Regressed
62	140/11	1.4	25	36	BE stage 1 zone 3	Biweekly follow up	Regressed
63	157/11	1.66	32	36	RE stage 3 zone 1,LE immature	Biweekly follow up	Regressed
64	145/11	1.7	30	36	BE stage 1 zone 3	Biweekly follow up	Regressed
65	162/11	1.2	32	36	RE stage 1 zone 3, 6-12’0 clock position, LE immature retina	Biweekly follow up	Regressed

SERIAL NO:	ROP REGISTRATION NUMBER	BIRTH WEIGHT	GESTATIONAL AGE	POST-CONCEPTIONAL AGE	DIAGNOSIS	TREATMENT/ FOLLOW UP	OUTCOME
66	161/11	1.3	32	42	BE stage 1,3 clock hours temporally	Biweekly follow up	Regressed
67	160/11	1.15	32	42	RE stage 1 zone 3,LE stage 1 zone 3	Biweekly follow up	Regressed
68	164/11	1.5	30	40	BE stage 1 zone 3	Biweekly follow up	Regressed
69	165/11	1.2	32	43	BE zone 3 mild tortuosity	Biweekly follow up	Regressed
70	162/11	1.2	32	37	BE stage 2 zone 3 6-12 o clock position	Biweekly follow up	Regressed
71	140/10	1.8	28	39	RE stage 2 zone 3 , LE stage 1, zone 3 2-4 o clock position	Biweekly follow up	Regressed
72	159/11	1.2	29	35	RE zone 3 7-11 0 clock, stage 1,LE zone 3, 1-5 o clock stage 1	Biweekly follow up	Regressed
73	169/11	1.5	32	35	RE zone 3 tortuos vessels	Biweekly follow up	Regressed

KEY:

RE - Right eye

LE - Left eye

BE - Both eye

ROP - Retinopathy of prematurity

ETROP - Early treatment of retinopathy of prematurity

ICROP - International classification of ROP

RD - Retinal detachment